

11/09/99



JC685 U.S. PTO

Patent
Attorney's Docket No. 012712-644

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

UTILITY PATENT
APPLICATION TRANSMITTAL LETTER



JC511 U.S. PTO
09/436348
11/09/99

Box PATENT APPLICATION
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Enclosed for filing is the utility patent application of Antonio J. GRILLO-LÓPEZ and John LEONARD for USE OF CHIMERIC ANTI-CD20 ANTIBODY AS *IN VITRO* OR *IN VIVO* PURGING AGENT IN PATIENTS RECEIVING BMT OR PBSC TRANSPLANT.

Also enclosed are:

- ☐ _____ sheet(s) of ☐ formal ☐ informal drawing(s);
- ☐ a claim for foreign priority under 35 U.S.C. §§ 119 and/or 365 is ☐ hereby made to _
filed in _ on _;
☐ in the declaration;
- ☐ a certified copy of the priority document;
- ☐ a General Authorization for Petitions for Extensions of Time and Payment of Fees;
- ☒ One statement(s) claiming small entity status;
- ☐ an Assignment document;
- ☐ an Information Disclosure Statement; and
- ☐ Other: _____.
- ☒ An ☐ executed ☒ unexecuted declaration of the inventor(s)
☒ also is enclosed ☐ will follow.
- ☐ Please amend the specification by inserting before the first line the sentence --This application claims priority under 35 U.S.C. §§119 and/or 365 to _ filed in _ on _; the entire content of which is hereby incorporated by reference.--
- ☐ A bibliographic data entry sheet is enclosed.



21839

☒ The filing fee has been calculated as follows [] and in accordance with the enclosed preliminary amendment:

CLAIMS					
	NO. OF CLAIMS		EXTRA CLAIMS	RATE	FEE
Basic Application Fee					\$760.00 (101)
Total Claims	6	MINUS 20 =	0	x \$18.00 (103)	0.00
Independent Claims	1	MINUS 3 =	0	x \$78.00 (102)	0.00
If multiple dependent claims are presented, add \$260.00 (104)					0.00
Total Application Fee					760.00
If verified Statement claiming small entity status is enclosed, subtract 50% of Total Application Fee					380.00
Add Assignment Recording Fee of if Assignment document is enclosed					0.00
TOTAL APPLICATION FEE DUE					380.00

- ☒ This application is being filed without a filing fee. Issuance of a Notice to File Missing Parts of Application is respectfully requested.
- [] A check in the amount of \$ _____ is enclosed for the fee due.
- [] Charge \$ _____ to Deposit Account No. 02-4800 for the fee due.
- [] The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800. This paper is submitted in duplicate.

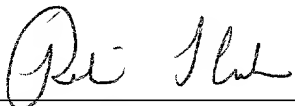
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Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: November 9, 1999

By: 
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66607 "STE" 6660

Applicant or Patentee: Antonio J. Grillo-López et al.

Application or Patent No.: _____

Filed or Issued: November 9, 1999

For: USE OF CHIMERIC ANTI-CD20 ANTIBODY AS *IN VITRO* OR *IN VIVO* PURGING AGENT
IN PATIENTS RECEIVING BMT OR PBSC TRANSPLANT

**VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 C.F.R. §§ 1.9(f) AND 1.27(c)) - SMALL BUSINESS CONCERN**

I hereby declare that I am

- ☐ the owner of the small business concern identified below:
☒ an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN IDEC PHARMACEUTICALS CORPORATION

ADDRESS OF CONCERN 11011 Torreyana Road, San Diego, CA 92121

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 C.F.R. § 1.21 for purposes of paying reduced fees under Sections 41(a) and 41(b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average, over the previous fiscal year of the concern, of the persons employed on a full-time, part-time, or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention entitled USE OF CHIMERIC ANTI-CD20 ANTIBODY AS *IN VITRO* OR *IN VIVO* PURGING AGENT IN PATIENTS RECEIVING BMT OR PBSC TRANSPLANT by inventor(s) ANTONIO J. GRILLO-LÓPEZ and JOHN LEONARD described in

- ☒ the specification filed herewith
☐ Application No. _____, filed _____
☐ Patent No. _____, issued _____

If the rights held by the above-identified small business concern are not exclusive, each individual, concern, or organization having rights to the invention is listed below,* and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 C.F.R. § 1.9(c), or by any concern that would not qualify as either a small business concern under 37 C.F.R. § 1.9(d) or a nonprofit organization under 37 C.F.R. § 1.9(e).

*NOTE: Separate verified statements are required from each named person, concern, or organization having rights to the invention averring to their status as small entities. (37 C.F.R. § 1.27.)

Application No. _____
Attorney's Docket No. 012712-644

NAME _____

ADDRESS _____

☐ individual ☐ small business concern ☐ nonprofit organization

NAME _____

ADDRESS _____

☐ individual ☐ small business concern ☐ nonprofit organization

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earlier of the issue fee and any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 C.F.R. § 1.28(b).)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING Christopher A. Dayton

TITLE OF PERSON OTHER THAN OWNER Assistant Secretary for Intellectual Property

ADDRESS OF PERSON SIGNING IDEC Pharmaceuticals Corporation

11011 Torreyana Road, San Diego, CA 92121

SIGNATURE _____ DATE _____

UNITED STATES PATENT APPLICATION

of

Antonio J. GRILLO-LÓPEZ

and

John LEONARD

for

USE OF CHIMERIC ANTI-CD20 ANTIBODY AS *IN VITRO*
OR *IN VIVO* PURGING AGENT IN PATIENTS RECEIVING
BMT OR PBSC TRANSPLANT

BURNS, DOANE, SWECKER & MATHIS, LLP
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ALEXANDRIA, VA 22313-1404

RELATED APPLICATIONS

This application claims benefit of priority to provisional application Serial No. 60/107,657, which is incorporated by reference in its entirety herein.

FIELD OF THE INVENTION

The use of an anti-CD20 antibody or a fragment thereof as an *in vitro* or *in vivo* purging agent in patients receiving bone marrow transplant or peripheral blood stem cell transplant is disclosed.

BACKGROUND OF THE INVENTION

The use of antibodies to the CD20 antigen as diagnostic and/or therapeutic agents for B-cell lymphoma has previously been reported. CD20 is a useful marker or target for B-cell lymphomas as this antigen is expressed at very high densities on the surface of malignant B-cells, i.e., B-cells wherein unabated proliferation can lead to B-cell lymphomas.

CD20 or Bp35 is a B-lymphocyte-restricted differentiation antigen that is expressed during early pre-B-cell development and remains until plasma cell differentiation. It is believed by some that the CD20 molecule may regulate a step in the B-cell activation process which is required for cell cycle initiation and differentiation. Moreover, as noted, CD20 is usually expressed at very high levels on neoplastic ("tumor") B-cells.

Previous reported therapies involving anti-CD20 antibodies have involved the administration of a therapeutic anti-CD20 antibody either alone or in conjunction with a second radiolabeled anti-CD20 antibody, or a chemotherapeutic agent.

In fact, the Food and Drug Administration has approved the therapeutic use of one such therapeutic anti-CD20 antibody, RITUXAN®, for use in relapsed and previously treated low-grade non-Hodgkin's lymphoma (NHL).

Also, the use of RITUXAN® in combination with a radiolabeled murine anti-CD20 antibody has been suggested for the treatment of B-cell lymphoma.

However, while anti-CD20 antibodies and, in particular, RITUXAN®, have been reported to be effective for treatment of B-cell lymphomas, such as non-Hodgkin's lymphoma, the treated patients are often subject to disease relapse. Therefore, it would be beneficial if more effective antibody treatments could be developed. More specifically, it would be advantageous if other therapeutic applications of anti-CD20 antibodies were discovered. Also, it would be helpful if current treatment protocols for B-cell lymphoma were improved, which prevented or further reduced disease relapse.

BRIEF DESCRIPTION OF THE INVENTION

Thus, it is an object of the invention to improve the problems of prior treatments of B-cell-related diseases, e.g., B-Cell lymphomas and leukemias, in particular the problem of disease relapse after disease treatment.

More specifically, it is an object of the invention to reduce the incidence of disease relapse in patients with B-cell-related diseases receiving bone marrow or peripheral blood stem cell transplants by the use of an anti-CD20 antibody as an *in vitro* and/or *in vivo* purging agent prior, concurrent, and/or after transplant.

It is an even more specific object of the invention to use RITUXAN® as an *in vitro* and/or *in vivo* purging agent prior, concurrent and/or after bone marrow or peripheral blood stem cell transplant.

DETAILED DESCRIPTION OF THE INVENTION

A significant problem associated with the treatment of diseases involving B-cells and other cells that express CD20 antigen, including B-cell lymphomas and leukemias, is the problem of disease relapse after treatment.

The exact cause for disease relapse is unclear. However, it is known that such relapse may occur even in patients that receive aggressive therapeutic intervention, e.g., high dosages of chemotherapeutic agents, cytokines, radiation, and/or antibody. While the exact cause of relapse remains unclear, it is speculated by some researchers that disease relapse may occur because the patient may still harbor low numbers of diseased cells even after aggressive therapy. Also, it is speculated that bone marrow transplant or peripheral blood stem cell transplanted tissue may itself be contaminated by diseased cells that express the CD20 antigen, e.g., B-cell lymphoma cells.

Therefore, transplant of such tissues may unwittingly introduce diseased cells, and thereby actually increase the risk of disease relapse.

As discussed, the present invention seeks to prevent or reduce the incidence of disease in patients receiving transplanted bone marrow or peripheral blood stem cells by treating the transplanted bone marrow or peripheral blood stem cells with an amount of an anti-CD20 antibody or fragment thereof effective to purge the transplanted tissue of disease-causing CD20 antigen-expressing cells. Such purging may be effected *in vitro* and/or *in vivo*.

For example, bone marrow or peripheral blood stem cells may be contacted in tissue culture with an anti-CD20 antibody prior to transplant. In the preferred embodiment such antibody will comprise a chimeric, primate, primatized®, humanized or human anti-CD20 antibody, preferably RITUXAN®.

Alternatively, or in conjunction with such *in vitro* purging, the patient may be treated concurrent or subsequent to bone marrow or peripheral blood stem cell transplant with an amount of an anti-CD20 antibody effective to purge (*in vivo*) or at least reduce the number of disease causing cells that express CD20 antigen that may be present in the transplant.

Similarly, the antibody used for *in vivo* purging will preferably comprise a chimeric, humanized, primate, primatized®, or human anti-CD20 antibody, preferably RITUXAN®. This *in vivo* purging may be effected simultaneous or

substantially contemporaneous to bone marrow or peripheral blood stem cell transplant. Preferably, such purging will be effected within a week or more, preferably within 1 to 12 hours after transplant. However, such purging can be effected up to about 1 to 100 days after transplant. In the preferred embodiment, *in vivo* purging will be effected within about 1 month after transplant, more preferably within about one week after transplant, and most preferably within about 1 to 12 hours after transplant.

As noted above, the subject *in vivo* or *in vitro* purging of CD20 antigen-expressing cells will desirably be effected in patients that have previously been treated in an effort to eradicate disease causing B-cells, or other CD20 antigen-expressing cells involved in disease. Such treatment methods include, by way of example, cytokine therapy, antibody therapies (e.g., RITUXAN® or other antibodies targeted to B-cells), chemotherapy and/or radiation therapy, e.g., whole body irradiation, radioimmunotherapy.

In an especially preferred embodiment, the subject *in vitro* or *in vivo* purging will be effected in patients that have previously been treated with RITUXAN® and/or radioimmunotherapy that receive an autologous bone marrow or peripheral blood stem cell transplant after RIT and/or RITUXAN® therapy.

For example, patients that have a B-cell-related disease, e.g., a B-cell lymphoma or leukemia, will have their bone marrow or peripheral blood stem cells collected prior to therapeutic treatment. This will be effected by known methods.

The patient will then be subjected to an aggressive therapeutic regimen, e.g., administration of RITUXAN®, or a radiolabeled antibody that is specific to an antigen expressed by the tumor cells, whole body irradiation, and/or a chemotherapeutic or cytokine. This therapeutic regimen will be effected under conditions that are hypothetically designed to eradicate any B-cell or other CD20 antigen-expressing tumor cells that may be present.

After such treatment has been completed, the bone marrow or peripheral blood stem cells, which optionally may be treated *in vitro* with an anti-CD20 antibody, e.g., RITUXAN®, to deplete CD20 expressing cells, is then transplanted into the patient in order to reconstitute the immune system thereof.

Concurrently or shortly thereafter, the patient will be administered an amount of an anti-CD20 antibody, e.g., RITUXAN®, effective to purge any disease causing cells that may be present in the bone marrow or peripheral blood stem cell transplant. An effective dosage will typically comprise from about 0.01 to about 3.0 mg/kg body weight. A preferred dosage will comprise from about .1 to about 20 mg/kg, more preferably from about .1 to about 5.0 mg/kg, administered within about one week of transplant.

The subject *in vitro* and/or *in vivo* purging will reduce the risk of relapse in many B-cell-related diseases, e.g., B-cell lymphomas and leukemias such as non-Hodgkin's lymphomas, chronic lymphocytic leukemia, etc., after treatment has been completed in patients receiving transplanted cells that potentially may be contaminated with disease-causing cells.

Also, the subject method should be well tolerated based on the relative non-toxicity of anti-CD20 antibodies, such as RITUXAN®, and therefore should not adversely impact engraftment of the transplanted autologous cells. In fact, it may act to promote engraftment of such transplant.

As noted in the preferred embodiment, the purging agent will comprise RITUXAN®. However, other anti-CD20 antibodies may be used, e.g., other chimeric, primate, primatized®, humanized or human antibodies. Also, antibody fragments may be used, e.g., Fv's, FAB, F(ab)'¹, F(ab₂)¹, and aggregates thereof. In addition, antibodies and antibody fragments directed to other B cell surface markers, e.g., CD19, may also be used.

Methods for producing chimeric, primate, primatized®, humanized and human antibodies are well known in the art. See, e.g., U.S. Patent 5,530,101, issued to Queen et al, U.S. Patent 5,225,539, issued to Winter et al, U.S. Patents 4,816,397 and 4,816,567, issued to Boss et al, and Cabilly et al, respectively, all of which are incorporated by reference in their entirety.

The selection of human constant regions may be significant to the therapeutic efficacy of the subject anti-CD20 antibody. In the preferred embodiment, the subject anti-CD20 antibody will comprise human, gamma 1, or gamma 3 constant regions and, more preferably, human gamma 1 constant regions. The use of gamma 1 anti-CD20 antibodies as therapeutics is disclosed in U.S. Patent 5,500,362, issued to Robinson et al.

Methods for making human antibodies are also known and include, by way of example, production in SCID mice, and *in vitro* immunization.

As noted, a particularly preferred chimeric anti-CD20 antibody is RITUXAN®, which is a chimeric gamma 1 anti-human CD20 antibody. The complete amino acid and corresponding nucleic acid sequence for this antibody may be found in U.S. Patent 5,736,137, which is incorporated by reference in its entirety. This antibody, which is produced in a proprietary CHO cell expression system commercialized by IDEC Pharmaceuticals Corporation, is made by a CHO cell transfectoma which was deposited on November 4, 1992, under the provisions of the Budapest Treaty at the American Type Culture Collection, located at 12301 Parklawn Drive, Rockville, MD 20852. This cell line was determined to be viable and will be replaced should it become non-viable during the term of deposit. This cell line was made irrevocably available upon issuance of the 5,736,137 patent and is available

without restriction from the ATCC. This cell line will also be available without restriction during the lifetime of any patent that may issue based on this application.

The subject anti-CD20 antibody, when used as a purging agent, will be administered by various routes of administration, typically parenteral. This is intended to include intravenous, intramuscular, subcutaneous, rectal, vaginal, and administration with intravenous infusion being preferred.

The anti-CD20 antibody will be formulated for therapeutic usage by standard methods, e.g., by addition of pharmaceutically acceptable buffers, e.g., sterile saline, sterile buffered water, propylene glycol, and combinations thereof.

EXAMPLE

A single-arm pivotal study of Rituximab® infused at 375 mg/m² weekly times four was conducted in 166 patients with relapsed or refractory, low-grade or follicular NHL (International Working Formulation [IWF] Types A - D and REAL classification, small lymphocytic lymphoma, Follicular center, follicular Grades I, II, III). (McLaughlin P, Grillo-López A, Link B, Levy R, Czuczman M, Williams M, Heyman M, Bence-Bruckler I, White C, Cabanillas F, Jain V, Ho A, Lister J, Wey K, Shen D, Dallaire B. Rituximab® chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a 4-dose treatment program. Journal of Clinical Oncology 1998; 16:2825-2833.) Patients with tumor masses > 10 cm or with > 5000 lymphocytes/μL in the peripheral blood

were excluded from this study. The median age was 58 years (105 men and 61 women) and the median number of prior treatments was three. Bone marrow involvement was present in 56% of 149 patients evaluated. Forty-five percent had ≥ 2 extranodal sites and 41% had bulky disease (≥ 5 cm).

Complete response required the regression of all lymph nodes to $< 1 \times 1$ cm² demonstrated on two occasions at least 28 days apart on neck, chest, abdomen, and pelvic CT scans, resolution of all symptoms and signs of lymphoma, and normalization of bone marrow, liver, and spleen. Partial response required a $\geq 50\%$ decrease in the sum of the products of perpendicular measurements of lesions without any evidence of progressive disease for at least 28 days. Patients who did not achieve a CR or PR were considered non-responders, even if a net decrease ($> 50\%$) of measurable disease was observed. Time to progression was measured from the first infusion until progression.

The overall response rate (ORR) was 48% with a 6% CR and a 42% PR rate (McLaughlin P, Grillo-López A, Link B, Levy R, Czuczman M, Williams M, Heyman M, Bence-Bruckler I, White C, Cabanillas F, Jain V, Ho A, Lister J, Wey K, Shen D, Dallaire B. Rituximab® chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a 4-dose treatment program. *Journal of Clinical Oncology* 1998; 16:2825-2833). The median time to progression (TTP) for responders was 13.2 months and the median duration

of response (DR) was 11.6 months. Twenty-two of 80 (28%) responders remain in ongoing remission at 20.9+ to 32.9+ months (McLaughlin P, Grillo-López A, Maloney D, Link B, Levy R, Czuczman M, Cabanillas F, Dallaire B, White C. Efficacy controls in long-term follow-up of patients treated with rituximab for relapsed or refractory, low-grade or follicular NHL. *Blood* 1998; 92:414a-415a).

Administration of Rituximab® resulted in a rapid and sustained depletion of B-cells. Circulating B-cells were depleted within the first three doses with sustained depletion for up to six to nine months post-treatment in 83% of patients. Median B-cell levels returned to normal by 12 months following treatment. Although median NK cell counts remained unchanged, a positive correlation was observed between higher absolute NK cell counts at baseline and response to Rituximab® (Janakiraman N, McLaughlin P, White C, Maloney D, Shen D, Grillo-López A. Rituximab: Correlation between effector cells and clinical activity in NHL. *Blood* 1998; 92 (10 Suppl 1):337a).

Several baseline prognostic factors were analyzed to determine their correlation to response. Significantly, in 23 patients relapsed after ABMT or PBSC, the ORR was 78% versus 43% in patients who did not undergo prior high-dose therapy ($p < 0.01$). This suggests that anti-CD20 treatment may effectively be used to purge CD20 antigen-expressing cells *in vivo* when administered following transplantation. Moreover, because patients who receive prior high dose therapy

accompanied a bone marrow or peripheral stem cell transplantation appear to benefit more from subsequent Rituximab® therapy than those patients without prior therapy and transplantation, this suggests that a combined treatment protocol including bone marrow or stem cell transplantation provides a synergistic effect when compared to either single treatment alone.

Although the present invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding it will be apparent that certain changes and modifications may be practical within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method for reducing the risk of relapse of a B-cell-related disease in a patient receiving a bone marrow or peripheral blood stem cell transplant comprising treating said transplant *in vitro* and/or *in vivo* with an amount of an anti-CD20 antibody effective to reduce (purge) the number of disease-causing CD20 antigen-expressing cells therein.

2. The method of Claim 1, wherein said disease is a B-cell lymphoma or leukemia.

3. The method of Claim 1, wherein said purging is effected *in vivo* by administering RITUXAN® no later than about one month after transplant.

4. The method of Claim 1, wherein RITUXAN® is administered at a dosage ranging from about 0.1 to 20 mg/kg about one week after transplant.

5. The method of Claim 4, wherein the patient receiving the transplant has previously been treated under conditions designed to eradicate disease-causing B-cells.

6. The method of Claim 4, wherein said patient has previously been subjected to a treatment protocol selected from the group consisting of whole body irradiation, RITUXAN® immunotherapy, chemotherapy, cytokine therapy, radioimmunotherapy, or a combination thereof.

ABSTRACT OF THE DISCLOSURE

The use of a chimeric anti-CD20 antibody, RITUXAN®, as an *in vivo* or *in vitro* purging agent, of patients receiving bone marrow or peripheral blood stem cell transplant during treatment of B-cell-related malignancies, e.g., B-cell lymphomas or leukemias, is disclosed. Such purging may enhance engraftment and/or prevent disease relapse in such patients.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to Provisional and PCT International Applications)

Attorney's Docket No.

012712-644

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

USE OF CHIMERIC ANTI-CD20 ANTIBODY AS *IN VITRO* OR *IN VIVO* PURGING AGENT IN PATIENTS

RECEIVING BMT OR PBSC TRANSPLANT

the specification of which (check only one item below):

☒ is attached hereto.

☐ was filed as United States application

Number _____

on _____

and was amended

on _____ (if applicable).

☐ was filed as PCT international application

Number _____

on _____

and was amended

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(e) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. §119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 U.S.C. §119
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

60/107,657
(Application Number)

November 9, 1998
(Filing Date)

(Application Number)

(Filing Date)

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONTINUED)
(Includes Reference to Provisional and PCT International Applications)

Attorney's Docket No.

012712-644

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Office all information known to me to be material to the patentability as defined in Title 37, Code of Federal Regulations §1.56, which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
PCT APPLICATIONS DESIGNATING THE U.S.				
PCT APPLICATION NO.	PCT FILING DATE	U.S. APPLICATION NUMBERS ASSIGNED (if any)		

I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:

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21839

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONTINUED) (Includes Reference to Provisional and PCT International Applications)		Attorney's Docket No. 012712-644	
FULL NAME OF SOLE OR FIRST INVENTOR Antonio J. GRILLO-LÓPEZ		SIGNATURE	
RESIDENCE P.O. Box 3797, Rancho Sante Fe, CA 92067		DATE	
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FULL NAME OF SECOND JOINT INVENTOR, IF ANY John LEONARD		SIGNATURE	
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FULL NAME OF THIRD JOINT INVENTOR, IF ANY		SIGNATURE	
RESIDENCE		DATE	
POST OFFICE ADDRESS		CITIZENSHIP	
FULL NAME OF FOURTH JOINT INVENTOR, IF ANY		SIGNATURE	
RESIDENCE		DATE	
POST OFFICE ADDRESS		CITIZENSHIP	
FULL NAME OF FIFTH JOINT INVENTOR, IF ANY		SIGNATURE	
RESIDENCE		DATE	
POST OFFICE ADDRESS		CITIZENSHIP	
FULL NAME OF SIXTH JOINT INVENTOR, IF ANY		SIGNATURE	
RESIDENCE		DATE	
POST OFFICE ADDRESS		CITIZENSHIP	
FULL NAME OF SEVENTH JOINT INVENTOR, IF ANY		SIGNATURE	
RESIDENCE		DATE	
POST OFFICE ADDRESS		CITIZENSHIP	
FULL NAME OF EIGHTH JOINT INVENTOR, IF ANY		SIGNATURE	
RESIDENCE		DATE	
POST OFFICE ADDRESS		CITIZENSHIP	
FULL NAME OF NINTH JOINT INVENTOR, IF ANY		SIGNATURE	
RESIDENCE		DATE	
POST OFFICE ADDRESS		CITIZENSHIP	